Guidelines for the use of Dapagliflozin (a SGLT2) in Heart Failure April 2021 (NICE TA679)

NHS
Bath and North East Somerset, Swindon and Wiltshire
Clinical Commissioning Group

NICE recommendation for use (NICE TA679):

Dapagliflozin is recommended as an option for treating symptomatic chronic heart failure with reduced ejection fraction <40% in adults, only if it is used as an add-on to optimised standard care with:

- angiotensin-converting enzyme (ACE) inhibitors or angiotensin-2 receptor blockers (ARBs), with beta blockers (BB), and, if tolerated, mineralocorticoid receptor antagonists (MRAs), or
- sacubitril valsartan, with beta blockers, and, if tolerated, MRAs.

Start treatment of symptomatic heart failure with reduced ejection fraction with dapagliflozin **on the advice of a heart failure specialist**. Monitoring should be done by the most appropriate healthcare professional.

Dapagliflozin for the treatment of heart failure has an AMBER traffic light status on the BSW formulary;
AMBER: These medicines are considered suitable for GP prescribing following specialist ***initiation or recommendation.*** (See ***http://www.bswformulary.nhs.uk/*** for further information).

General points for use:

- The recommended dose of dapagliflozin for heart failure is **10 mg once daily**.
- The specialist team (consultant or nurse) should check the patient's HbA1c before initiating dapagliflozin (if there are no recent results for this) to ensure the patient doesn't have undiagnosed diabetes.
- Medical notes need to be very clear as to the **indication for use** when this is initiated, as there is a risk that someone reviewing the medication might stop the dapagliflozin if the patient has type 2 diabetes with renal function deteriorating. This will also help local acute trusts in terms of knowing what to do with respect to the medication when a patient is acutely unwell.
- Although it is recognised that the beneficial effects of sodium-glucose cotransporter 2 inhibitors (SGLT2s) in heart failure is probably a class effect, all **NEW** pts requiring a SGLT2 inhibitor for heart failure should receive dapagliflozin so that the GP is prescribing a licensed medicine.
- Where possible, the first one month prescription supply will be provided by the specialist. It is recognised that this might not always be possible due to practicalities. If so, the GP might be asked to initiate dapagliflozin via written advice from the specialist.

Sequencing of heart failure therapy[1]

- Large-scale trials have demonstrated the efficacy of ACE-inhibitors/ARB or sacubitril/valsartan, β-blockers, MRAs, and SGLT2 inhibitors as disease-modifying agents that (when combined) represent foundational therapy for heart failure and a reduced ejection fraction (HFrEF).
- Although the NICE NG106 (Sept 2018) advises that drugs are initiated individually and doses optimised before adding another drug group into treatment, current theory is that any delay in starting the above groups of heart failure drugs is not acceptable because each of the foundational drugs has been shown to reduce morbidity and mortality within 30 days of initiating treatment. With every passing visit, the absence of ≥1 therapy results in unnecessary hospitalizations and deaths. Therefore local specialists are moving towards getting patients onto drugs from each of these 4 drug classes as quickly as possible. Up-titration to target doses would be pursued thereafter. Local treatment guidance for heart failure is being produced to support local prescribers about this.
- The addition of a new drug class yields benefits that are greater in magnitude than up-titration of existing drug classes. Indeed, 3- to 7-fold increments in the dose of an ACE-I or ARB produces none of the mortality reduction seen with the addition of a β-blocker, neprilysin inhibitor, or SGLT2 inhibitors.
- The proper sequencing of drug classes can improve safety and tolerability. Specifically, neprilysin inhibition can reduce the risk of renal insufficiency produced by an ACE-I or ARB, and both neprilysin inhibitors and SGLT2 inhibitors can minimize the risk of hyperkalemia seen with the use of MRAs.

Developed in consultation with CV specialists/Diabetologists/Renal specialist from North Bristol trust and BSW. BSW CCG Medicines Optimisation April 2021

Guidelines for the use of Dapagliflozin (a SGLT2) in Heart Failure April 2021 (NICE TA679)

NHS
Bath and North East Somerset, Swindon and Wiltshire
Clinical Commissioning Group

Use of Dapagliflozin in renal impairment

Be aware that the renal threshold for reviewing dapagliflozin differs according to the indication for use. The table below highlights the different thresholds in the licenses for the different SGLT2 inhibitors (see individual SPC links in further information section page 4 for full information):

Drug	Renal threshold to review (type 2 diabetes)	Renal threshold to review (HF)
Dapagliflozin	GFR 45ml/min	GFR 30ml/min
Canagliflozin	Use lower 100mg dose if eGFR 30-60ml/min	N/A
Empagliflozin	eGFR 45ml/min	N/A
Ertugliflozin	eGFR 45ml/min	N/A

When SGLT2 inhibitors are used to treat type 2 diabetes, it is the anti-diabetic effect that weakens, which leads towards the recommendations to review use at higher renal thresholds, it is not due to concerns about the safety of their use in renal impairment. There is significant clinical trial data regarding the use of SGLT2 inhibitors in low renal function, such as DAPA-CKD[2] which used dapagliflozin down to a eGFR of 25ml/min, DAPA-HF[3] which went down to an eGFR of 30ml/min and canagliflozin (CREDENCE[4]) down to a eGFR of 30ml/min.

Empagliflozin is expected to receive a license for heart failure in Q4 2021 after the positive data from the EMPEROR-Reduced trial[5] and dapagliflozin is expected to receive a license for treatment of chronic kidney disease in the financial year 21-22.

Please note that if a patient starts to see a decline their renal function to below 30ml/min whilst on Dapagliflozin, **do not stop treatment** without a discussion with the heart failure specialist first of all.

Use of Dapagliflozin for heart failure in type 2 diabetes

If a type 2 diabetic patient is seen by a heart failure specialist already on a SGLT2 inhibitor which isn't dapagliflozin, and their renal function is comfortably above an eGFR of 60ml/min, there is no rush to switch them to dapagliflozin. This is due to the class heart failure effect. A license for Empagliflozin for heart failure is due in Q4 2021.

If however, the patient does have an eGFR close to 60ml/min or below, it might be worth reviewing the alternative SGLT2 inhibitor and switching them to dapagliflozin in order to allow the GP to prescribe a licensed medicine for that renal function. It would also help to reduce confusion as to what indication the patient is on the SGLT2 inhibitor for. There is a risk that someone reviewing a patient's diabetes medicines could wrongly stop alternative SGLT2 inhibitors if they think they were on it for their type 2 diabetes, when the patient has actually been left on it because of its effect on their heart failure.

When a cardiologist is considering initiating dapagliflozin in a type 2 diabetes patient they may need to refer the patient for advice when initiating dapagliflozin as per the following table in order to ensure that the anti-diabetic effect of the dapagliflozin is considered amongst other concurrent anti-diabetes medications. Such patients may need to increase their frequency of blood glucose testing initially when dapagliflozin is started to identify any resulting hypoglycaemia:

Medication	Refer to
Type 2 diabetic patient on insulin	DSN
Type 2 diabetic patient on SU/repaglinide	GP
Type 2 diabetic patient on metformin alone	Cardiologist can initiate themselves

Use of Dapagliflozin for heart failure in type 1 diabetes

Use in type 1 diabetic patients is not recommended in the SPC. There is no data available on the use of dapagliflozin for heart failure in such patients, the dose used in HF is above the maximum dose licensed for use in type 1 diabetes (5mg OD) and there is a much higher diabetic ketoacidosis (DKA) risk. If a heart

failure specialist wishes to consider the use of dapagliflozin in a type 1 patient, they will need to discuss with a diabetologist and it would need to be prescribed by the specialist long-term, as the formulary positioning in type 1 patients is RED.

Other considerations when initiating Dapagliflozin

Concomitant diuretics: Diuretics are sometimes used in heart failure patients for symptomatic control. SGLT2 inhibitors have a mild diuretic effect and so the specialist will review the use and dose of concurrent diuretics to ensure that the small additive effect of the SGLT2 inhibitor does not cause untoward problems. Many patients will be able to continue their diuretics if they are needed, but care may be needed in the elderly or frail.

Symptomatic hypotension or systolic blood pressure < 95 mmHg: This is more often a problem due to other medications that the patient is taking. Having a systolic BP <95mm Hg is NOT a contra-indication for use. The specialist will carefully review the patients and their medications when initiating dapagliflozin but it is not expected that there will be problems initiating dapagliflozin in most patients with a blood pressure like this. Care will be needed if a patient is experiencing dizziness prior to initiation.

Renal function decline upon initiation of dapagliflozin: After initiation of treatment with dapagliflozin the eGFR often dips but this usually resolves in 1-3 months. There is no need to monitor U&Es specifically for this.

Dapagliflozin should not be used in patients on a very carbohydrate restricted diet (eg atkins).

Safety considerations for GPs: (See SPCs for full information)

Volume depletion: In case of intercurrent conditions that may lead to volume depletion (e.g. gastrointestinal illness), careful monitoring of volume status (e.g. physical examination, blood pressure measurements, laboratory tests including haematocrit and electrolytes) is recommended. Temporary interruption of treatment with dapagliflozin is recommended for patients who develop volume depletion until the depletion is corrected.

Treatment should be interrupted in patients who are hospitalised for major surgical procedures or acute serious medical illnesses as advised by the specialist.

DKA risk: SGLT2 inhibitors should be used with caution in patients with increased risk of DKA. Patients who may be at higher risk of DKA include those with a low beta-cell function reserve (e.g. type 1 diabetes, type 2 diabetes with low C-peptide or latent autoimmune diabetes in adults (LADA) or those with a history of pancreatitis). Also patients with conditions that lead to restricted food intake or severe dehydration, patients for whom insulin doses are reduced and patients with increased insulin requirements due to acute medical illness, surgery or alcohol abuse.

STOP Dapagliflozin:

- In patients where DKA is suspected or diagnosed.
- In patients with intercurrent illness if not eating or at risk of dehydration and only restart once better and back on normal diet.
- In patients admitted to hospital acutely unwell for any reason and restart only once fully recovered and eating and drinking normally.
- In any patient having elective surgery who is missing more than one meal and restart only once recovered and eating and drinking normally

Restarting SGLT2 inhibitor treatment in patients experiencing a DKA while on SGLT2 inhibitor treatment is **not recommended**, unless another clear precipitating factor is identified and resolved. Specialist advice should be sought.

Urinary tract infections*:* Urinary glucose excretion may be associated with an increased risk of urinary tract infection; therefore, temporary interruption of dapagliflozin should be considered when treating pyelonephritis or urosepsis.
Vulvovaginitis, balanitis and related genital infections: Listed as "common" in SPC.

If a patient has a deterioration in their heart failure symptoms (e.g. increasing breathlessness and fluid retention) then the GP will need to seek further advice from the specialist.

Patient advice

This patient information has been produced by the manufacturer and can be used to counsel patients on what they need to watch out for: Forxiga-Heart-Failure-Patient-Booklet-Updated.pdf (includes sick day rules).
Advise patient against having a very carbohydrate restricted diet (eg atkins) –dapagliflozin should not be started in such patients.

Further information for health care professionals

- Forxiga (dapagliflozin) Information for UK Healthcare Professionals
- MHRA April 2016 -SGLT2 inhibitors: updated advice on the risk of diabetic ketoacidosis
- MHRA Feb 2019 - SGLT2 inhibitors: reports of Fournier's gangrene (necrotising fasciitis of the genitalia or perineum)
- MHRA March 2017 - SGLT2 inhibitors: updated advice on increased risk of lower-limb amputation (mainly toes)
- SPC for Canagliflozin: https://www.medicines.org.uk/emc/product/11409/smpc
- SPC for Dapagliflozin: https://www.medicines.org.uk/emc/product/7607/smpc
- SPC for Empagliflozin: https://www.medicines.org.uk/emc/product/5441/smpc
- SPC for Ertugliflozin: https://www.medicines.org.uk/emc/product/10099/smpc

References

1. McMurray JJV and Packer M. How should we sequence the treatments for heart failure and a reduced ejection fraction? A redefinition of evidence-based medicine. Circulation. March 2nd 2021; 143:875-877. https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.120.052926
2. Heerspink HJL et al. Dapagliflozin in patients with chronic kidney disease. N Engl J Med 2020; 383:1436-1446. https://www.nejm.org/doi/full/10.1056/NEJMoa2024816
3. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med 2019; 381: 1995-2008. https://www.nejm.org/doi/full/10.1056/NEJMoa1911303
4. Perkovic V et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Eng J Med 2019; 380:2295-2306. https://www.nejm.org/doi/full/10.1056/nejmoa1811744
5. Packer M et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. N Engl J Med 2020; 383:1413-1424. https://www.nejm.org/doi/full/10.1056/NEJMoa2022190

Contact Details

- **RUH:** Dr Jacob Easaw (Consultant cardiologist) secretary: 01225 821937
- **SFT:** Sally Brown, sec to Dr Tom Jackson (Consultant Cardiologist) 01722 336262 ext 2961
- **GWH:** 01793 604273
- **GWH community heart failure service:** Rachel Hurt and Martin Larner: 01793 605921 or GWH.HeartFunctionTeam@nhs.net
- **BaNES heart Failure Service: 01225 396060 (Mon-Fri) or vcl.bathneshfs@nhs.net**

Developed in consultation with CV specialists/Diabetologists/Renal specialist from North Bristol trust and BSW. BSW CCG Medicines Optimisation April 2021